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Solid Separation from a Mixed Suspension through Electric-Field-Enhanced Crystallization

Wei W. Li, Norbert Radacsi, Herman J. M. Kramer, Antoine E. D. M. van der Heijden, and Joop H. ter Horst*

Abstract: ■■ Title change ok? ■■ When applied to a pure component suspension in an apolar solvent, a strong inhomogeneous electric field induces particle movement, and the particles are collected at the surface of one of the two electrodes. This new phenomenon was used to separately isolate two organic crystalline compounds, phenazine and caffeine, from their suspension in 1,4-dioxane. First, crystals of both compounds were collected at different electrodes under the influence of an electric field. Subsequent cooling crystallization enabled the immobilization and growth of the particles on the electrodes, which were separately collected after the experiment with purities greater than 91 %. This method can be further developed into a technique for crystal separation and recovery in complex multicomponent suspensions of industrial processes.

Crystallization is an effective and efficient separation technology that can, in a single process step, recover desired compounds from solutions as high-purity (> 99 %) crystalline solids.^[1–4] However, such very pure products are difficult to obtain from a multicomponent solution, such as the product stream from a type-I multicomponent reaction (MCR)^[5,6] or a racemic mixture of chiral pharmaceutical compounds,^[7] by direct crystallization as a mixed suspension is a likely result. Further purification of the solid phase usually requires additional steps (see Figure 1a), which will inevitably lead to the loss of valuable products. Alternatively, a single crystallization step coupled with simultaneous particle separation could diminish the product loss while enabling the effective recovery of a desired solute from a mixed solution.

Particle manipulation and subsequent separation can be achieved by the application of electromagnetic fields: A magnetic field can separate polymorphs (crystalline solids with different solid-state structures) to prepare seeds for large-scale crystallization provided that a suitable paramag-

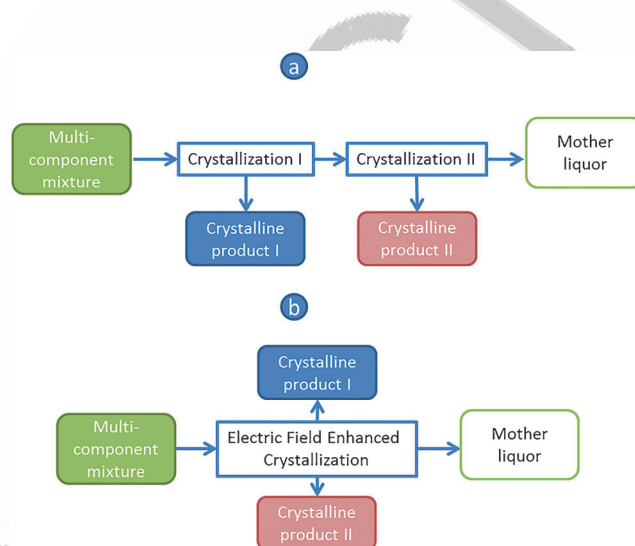


Figure 1. Solute separation from a multicomponent solution by direct crystallization (a) and electric-field-enhanced crystallization (b).

netic medium can be found.^[8] Alternatively, an electric field has been used for the capture and manipulation of nanoparticles^[9] and the assembly of colloid particles for the production of optically tunable micropatterns, biosensors, and biofuel cells, for example.^[10–12] In all of these cases, the liquid phases did not contain any dissolved particle materials. On the other hand, electric fields have been used to localize protein crystallization and control its nucleation rate from a clear solution in the absence of any seed crystals.^[13,14] However, to date, the combination of particle manipulation by an electric field with a crystallization process for in situ product separation and recovery has, to the best of our knowledge, never been attempted. Herein, experimental proof is given for an electric-field-enhanced crystallization (EEC) process by which the two solutes from a multicomponent solution are separately recovered (Figure 1b).

When subjected to an inhomogeneous electric field, particles in a suspension experience dielectrophoretic (DEP) and possibly electrophoretic (EP) forces: DEP forces originate from the difference in the dielectric constants of the particles and the surrounding medium and drag the particles with the larger dielectric constant towards the location of the electric-field maxima,^[15,16] while EP forces, which work only on charged particles, are directed towards the electrode with the opposite charge.^[17] To prevent electrochemical reactions, which would reduce the product yield, the current passed through a crystallizing suspension should be minimized. Meanwhile, the inhomogeneous field needs to be

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sufficiently strong, and the dielectric constant of the solvent sufficiently small, to ensure the effective manipulation of crystals by the DEP force. Therefore, the apolar and non-conductive solvent 1,4-dioxane was used in this study.

We first applied an inhomogeneous electrostatic field to a 6 mL isonicotinamide (INA) suspension in 1,4-dioxane (ca. 18 mg solid per mL solvent), which was generated by a direct current (DC) potential difference between two parallel rod-shaped electrodes about 6 mm apart, which were immersed into the suspension. In the presence of a DC potential difference above approximately 2 kV, INA crystals started to move around the electrodes. More crystals participated in this circular movement with increasing potential difference. Furthermore, INA crystals gradually accumulated on the anode (Figure 2). Above a DC potential difference of about

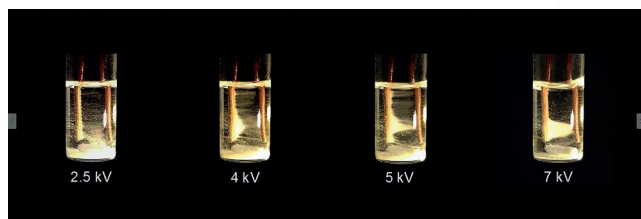


Figure 2. An inhomogeneous static electric field induced fluid and particle dynamics above a DC potential difference of 2 kV in a suspension of INA in 1,4-dioxane. The INA crystals were collected at the anode, and above a DC potential difference of about 5 kV, a crystal bridge was formed between the electrodes. Although a magnetic stirrer bar was present in the vial, it was not used to stir the solution.

5 kV, the amount of crystals collected at the anode was so large that a crystal bridge formed between the electrodes. Upon switching off the electric field, the collected crystals detached from the anode and moved back to the bottom. When a similar potential difference was applied to an INA solution in the absence of crystals, the solution–air interface was only slightly vibrating. No movement of liquid could be observed in pure 1,4-dioxane. This indicates that the motion of INA particles is, for a large part, related to the interaction of the crystals with the electric field. During the course of these experiments, no current larger than the detection limit of 0.01 mA was observed. No gas formation could be observed on either of the electrodes, indicating that the solute does not undergo significant electrochemical reactions.

Equivalent experiments were conducted with suspensions of other organic compounds in 1,4-dioxane. Table 1 reveals an interesting result: Particle motion was induced in all cases, and crystals accumulated on either the anode or the cathode. When the polarity of the two electrodes was reversed by changing the potential difference from +7.5 kV to −7.5 kV, crystals that had accumulated on one electrode migrated to the other one; for example, INA crystals moved from the old anode to the new one instead of being attracted by both electrodes, which were symmetrically the two locations of field maxima. ■■■ meaning unclear? ■■■

This selective accumulation of crystals on only one electrode indicates the involvement of both DEP and EP forces: The non-uniform electrostatic field exerts a positive

Table 1: The electrodes at which the crystals accumulated in experiments in which inhomogeneous electric fields of +7.5 and −7.5 kV were applied to suspensions of various organic compounds in 1,4-dioxane. Upon changing the polarity, the crystals accumulated on the electrode that is electrochemically the same; that is, INA crystals moved to the new anode, for example.

Electrode	Crystalline compound ^[a]		
Anode	INA	NIF	CAF
Cathode	PHE	HBA	

[a] CAF = caffeine, HBA = 4-hydroxybenzoic acid, INA = isonicotinamide, NIF = niflumic acid, PHE = phenazine.

DEP on the crystals in the suspension, which triggers their motion towards the two electrodes. Even in apolar solvents, particle surfaces can be slightly charged^[18–20] but the EP forces on the crystals become significant only in the vicinity of the electrodes. Crystals approaching the anode are further attracted until they settle on its surface while crystals close to the cathode are repelled. The repelled crystals continue to circulate until they are eventually captured by the anode. Subsequently, the entire crystalline mass accumulates on the surface of the anode. As particulate materials differ in their electronic properties, such as the dielectric constant and surface charge, the combined effect of DEP and EP forces can lead to the accumulation of the corresponding crystals on different electrodes, which enables the development of particle separation methods.^[21–24]

However, in order to be collected from the solution, the accumulated crystals need to be immobilized on the electrode. This immobilization of crystals was realized by slowly cooling the suspension in the presence of the electric field. Upon cooling, the solubility decreased, and the accumulated particles could further grow on and adhered to the electrode surface. Two separate experiments (see Figure 3, ■■■Figures renumbered. ok? ■■■ experiments 1A and 1B) were performed on pure component suspensions of the model compounds phenazine (PHE) and caffeine (CAF). ■■■ok? ■■■

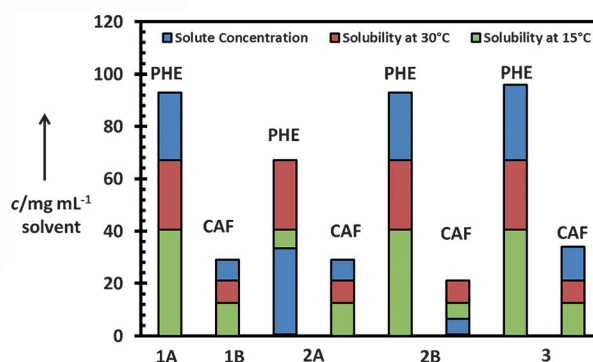


Figure 3. Concentrations and solubilities at 15 °C and 30 °C of PHE and CAF in all experiments.

In experiment 1A, a suspension of PHE (ca. 26 mg solid per ml solvent) was prepared at 30 °C (see the Supporting Information for details). A DC potential difference of −7.5 kV was then applied between the two electrodes, and

the PHE crystals accumulated at the cathode surface within 1 min. In the presence of the electric field, the suspension was slowly cooled down in an oil bath to 15 °C in 3 h and then kept at this temperature overnight to allow for crystal growth. After approximately 15 h at 15 °C, the electric field was turned off; most of the PHE crystals were attached to the cathode surface (Figure 4, left) and could be directly removed from the solution by withdrawing the electrode. The same procedure was applied to a CAF suspension in experiment 1B, and the corresponding crystals were collected from the anode (not shown).

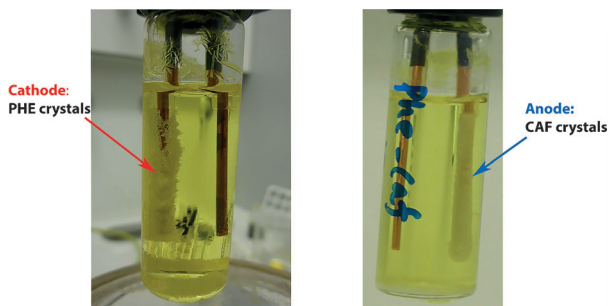


Figure 4. Left: PHE crystals accumulated and then adhered to the cathode in a PHE suspension in 1,4-dioxane after cooling in the presence of an electric field (experiment 1A). Right: Suspended CAF crystals in a solution containing both CAF and PHE accumulated and then adhered to the anode during seeded cooling crystallization controlled by an electric field (experiment 2A).

Furthermore, the presence of another solute in the solution phase (see Figure 3, experiments 2A and 2B and the Supporting Information) did not influence the behavior of the suspensions in the electric field. Similar to experiment 1B, in experiment 2A, CAF crystals were collected from the anode after cooling crystallization to 15 °C under the electric field from a solution with additional PHE present below its saturation concentration (Figure 4, right). XRPD analysis of the crystalline product revealed the presence of CAF crystals only (see the Supporting Information). These experiments confirmed that the electric-field-induced particle capture combined with cooling crystallization can be used as an in situ recovery technique for a target system where only one compound is present in the solid phase.

At this point, the EEC process could be used to collect crystals of PHE and CAF from their suspensions, with or without the presence of another solute in the liquid phase. The final step then was to confirm that PHE and CAF crystals can also be separated during crystallization from their mixture by EEC. ■■■ok?■■■ A 6 mL 1,4-dioxane suspension containing both CAF (ca. 13 mg solid per ml solvent) and PHE (ca. 29 mg solid per ml solvent) crystals was prepared at 30 °C (experiment 3 in Figure 3; see the Supporting Information for details). In the presence of a -7.5 kV DC potential difference, crystals accumulated on the surfaces of both electrodes at 30 °C (Figure 5, left). The suspension was then linearly cooled down to 15 °C in 3 h and kept at this temperature overnight while the electric field was kept constant. ■■■ok?■■■ Crystal layers of different shapes

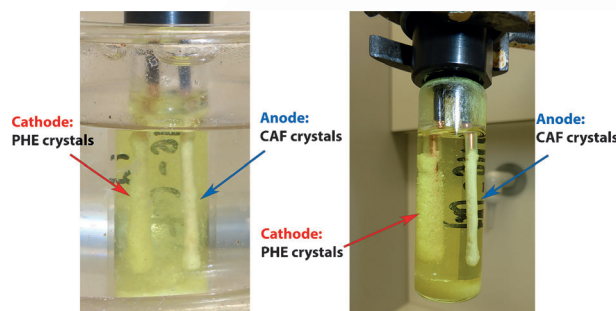


Figure 5. Crystals accumulated on both electrodes (left) upon applying an inhomogeneous electric field to a mixed suspension of CAF and PHE in 1,4-dioxane at 30 °C. After cooling in the presence of the electric field, crystal layers of different color, shape, and thickness were collected from the two electrodes at 15 °C. Some crystals remained at the bottom of the vial (right).

and colors were formed on both electrodes, reflecting the appearance of PHE (cathode) and CAF (anode) crystalline phases (Figure 5, right).

The crystals from the two electrodes were removed from the bulk solution, separately weighed for yield estimation, and then analyzed by XRPD and ¹H NMR spectroscopy to determine their compositions. From the anode, 27 mg of crystalline material was recovered, which consisted of 91.4 ± 2.2 wt % CAF. From the cathode, 177 mg of crystalline material was recovered, which consisted of 99.6 ± 2.4 wt % PHE (see the Supporting Information). The recovery yields for CAF and PHE were 20.9% and 53.5%, respectively (Figure 6). The same experiment was duplicated, and lower yields but similar solid-phase purities to those reported above were obtained. This result confirmed that the combination of selective particle collection, induced by an inhomogeneous electric field, with cooling crystallization can indeed be used to separate and simultaneously remove two compounds from their mixture. ■■■ok?■■■

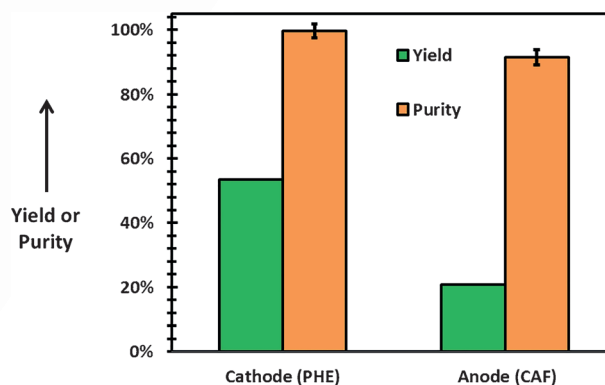


Figure 6. Yield and purity of PHE (cathode) and CAF (anode) crystals recovered in experiment 3. ■■■ok?■■■

In conclusion, a separation technique that is based on coupling particle manipulation by an inhomogeneous electrostatic field and cooling crystallization, here referred to as electric-field-enhanced crystallization (EEC), has been devel-

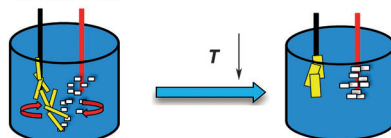
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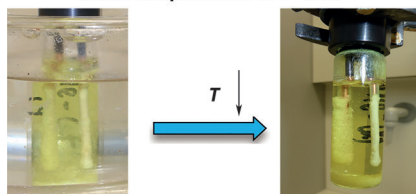
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Electric Field



Mixed suspension PHE + CAF



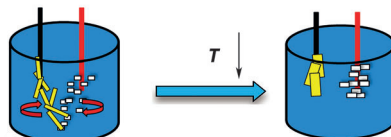
Crystallization from a multicomponent mixture requires additional steps for product purification. The application of an inhomogeneous electric field on a mixed suspension enables simultaneous particle separation and crystal growth. Crystals of the two solutes (CAF = caffeine, PHE = phenazine) are then separately collected from the two electrodes.

Trenntechnik

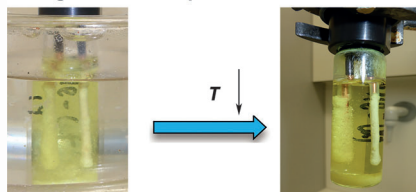
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elektrisches Feld



gemischte Suspension PHE + CAF



Bei Kristallisationen aus Mehrkomponentenmischungen sind weitere Schritte für die Produktreinigung nötig. Wird an einer gemischten Suspension jedoch ein inhomogenes elektrisches Feld angelegt, können Partikelabtrennung und Kristallwachstum in einem Schritt durchgeführt werden. Kristalle der zwei gelösten Substanzen (CAF = Kaffein, PHE = Phenazin) sammeln sich getrennt an den zwei Elektroden an.

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